Przeciwciała monoklonalne w nefrologii

Wybrane problemy

Jacek Zachwieja

Klinika Kardiologii i Nefrologii Dziecięcej

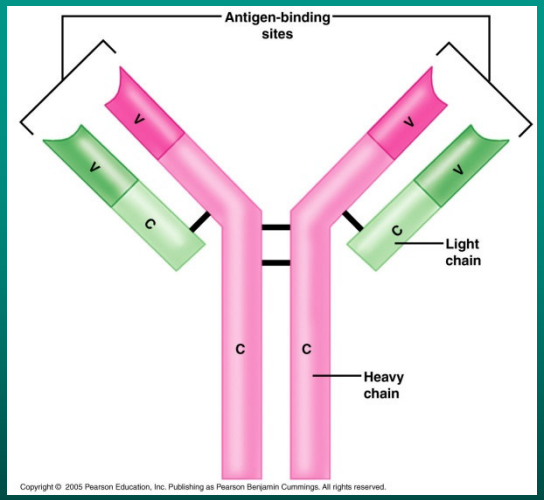
Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu

Przeciwciała monoklonalne

Grupa leków biologicznych

Immunoglobuliny

- IgG
- 2 łańcuchy ciężkie
- 2 łańcuchy lekkie
- części stałe
- części zmienne



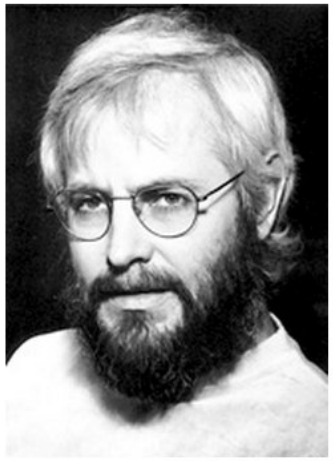
Nobelprize.org
The Official Web Site of the Nobel Prize

The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne, Georges J.F. Köhler, César Milstein

- **The Nobel Prize in Physiology or Medicine 1984**
- Nobel Prize Award Ceremony
- Niels K. Jerne
- Georges J.F. Köhler
- César Milstein

Niels K. Jerne



Georges J.F. Köhler

César Milstein

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein *"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"*.

Przeciwciała monoklonalne

ROLA:

modyfikowanie reakcji immunologicznych

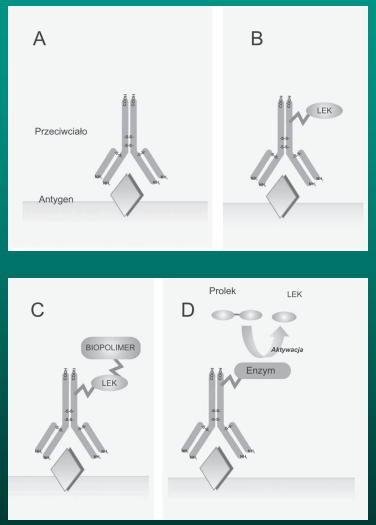
Przeciwciała monoklonalne

Modyfikowanie reakcji immunologicznych:

deplecja

hamowanie funkcji

transport leków/enzymów (DDS)



Przeciwciała monoklonalne

Nowości:

mAbs biswoiste

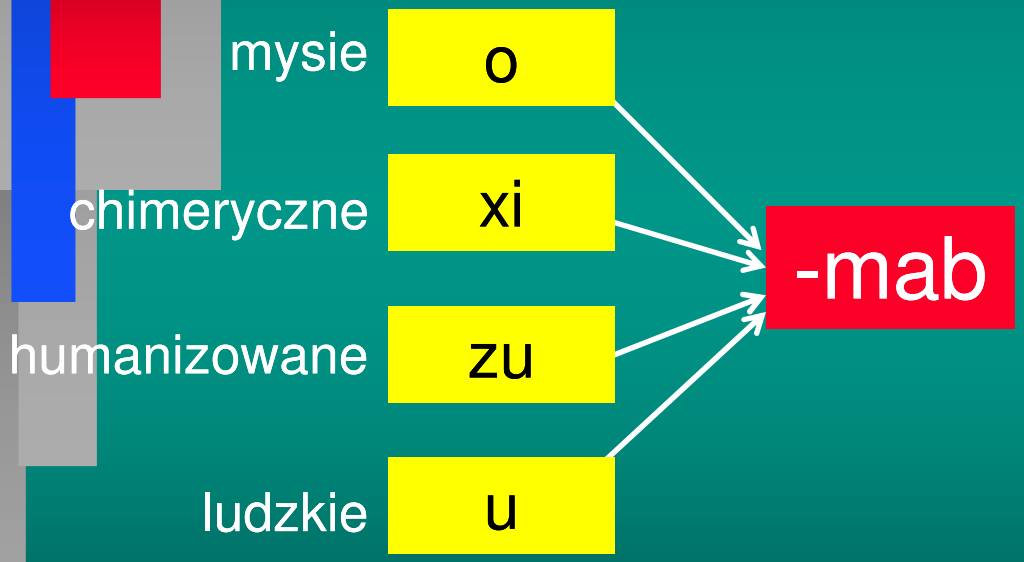
mAbs o zmniejszonej masie

immunokoniugaty

Przeciwciała monoklonalne

mAb mysie	mAb chimeryczne	mAb humanizowane	mAb ludzkie
100% struktury mysiej	ok. 65–90% struktury ludzkiej	ok. 90% struktury ludzkiej	100% struktury ludzkiej

Przeciwciała monoklonalne



adrenocolo**mab**

infli**ximab**

bewaci**zumab**

adalim**umab**

Białka fuzyjne

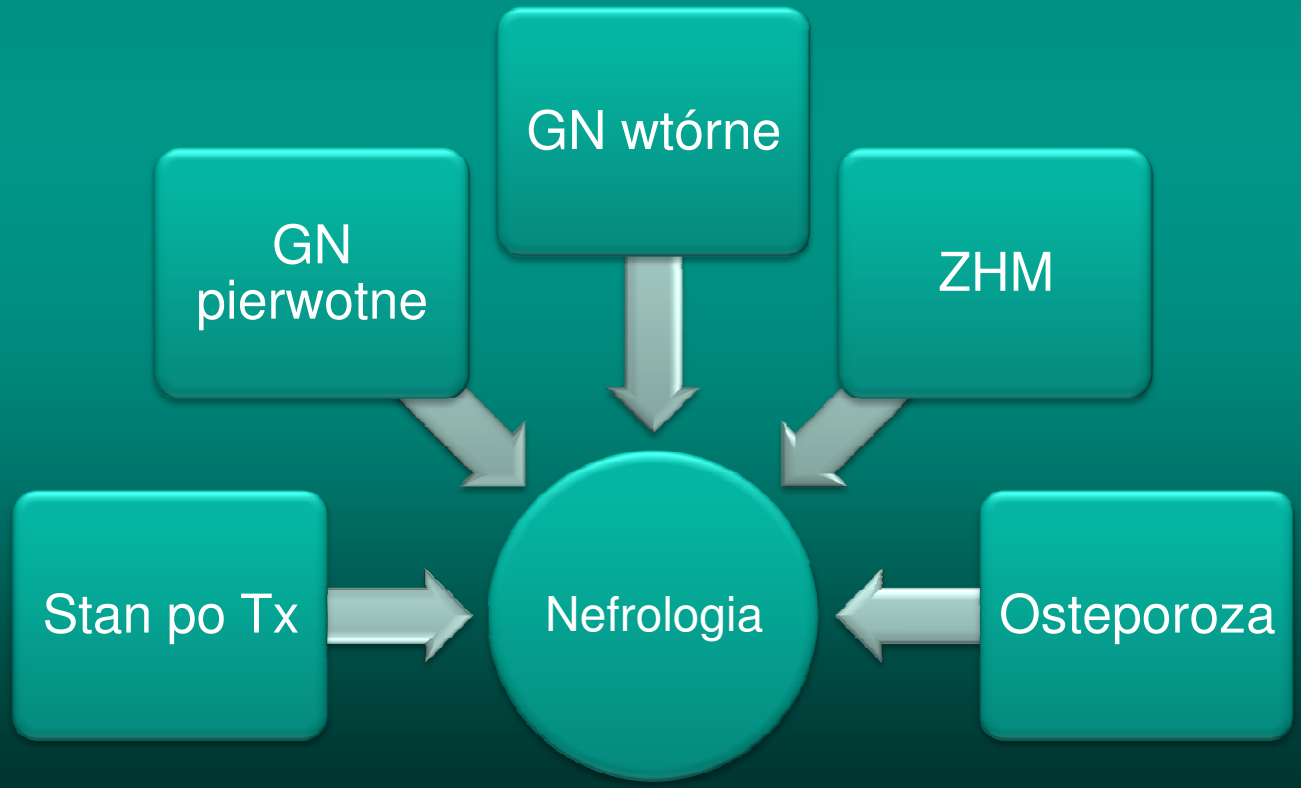
-cept

etaner**cept**

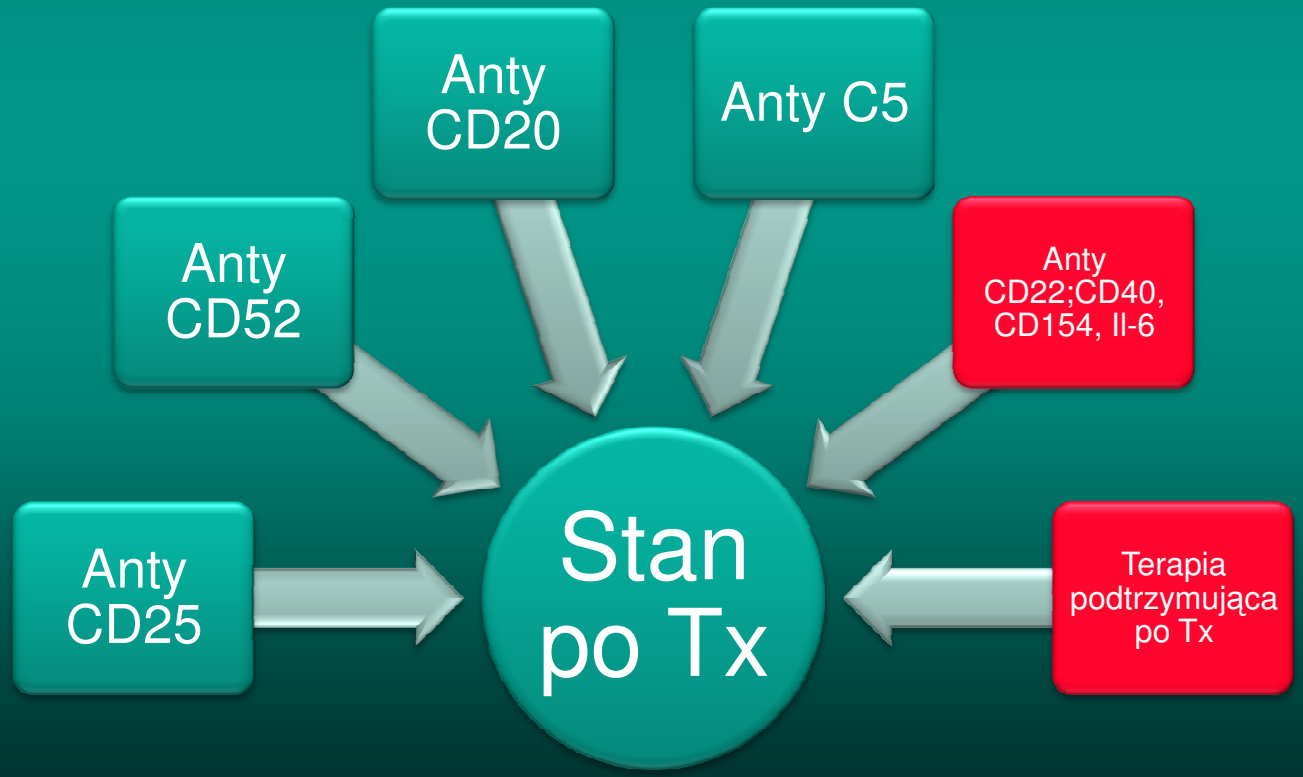
Nazwa międzynarodowa	Nazwa handlowa	Cel molekularny; rodzaj przeciwciała	Wskazanie terapeutyczne	Rejestracja
Ofatumumab	Arzerra	CD20; ludzkie IgG1	przewlekła białaczka limfocytarna	2009
Tositumomab-I^{131}	Bexxar	CD20; mysie IgG2a	chłoniak nieziarniczy	2003
Ibritumomab-tiuxetan	Zevalin	CD20; mysie IgG1	chłoniak nieziarniczy	2002
Rituximab	Rituxan	CD20; chimeryczne IgG1	chłoniak nieziarniczy	1997
Gemtuzumab ozogamicin	Mylotarg	CD33; humanizowane IgG4	ostra białaczka szpikowa	2000*
Alemtuzumab	Campath-1H	CD52; humanizowane IgG1	ostra białaczka szpikowa	2001
Panitumumab	Vectibix	EGFR; ludzkie IgG2	rak jelita	2006
Cetuximab	Erbitux	EGFR; chimeryczne IgG1	rak jelita	2004
Trastuzumab	Herceptin	HER2; humanizowane IgG1	rak piersi	1998
Bevacizumab	Avastin	VEGF; humanizowane IgG1	rak jelita	2004
Eculizumab	Soliris	C5; humanizowane IgG2/4	napadowa nocna hemoglobinuria	2007
Muromonab-CD3	Orthoclone OKT3	CD3; mysie IgG2a	profilaktyka reakcji odrzucenia przeszczepu	1986*
Basiliximab	Simulect	IL2R; chimeryczne IgG1	profilaktyka reakcji odrzucenia przeszczepu	1998
Dadizumab	Zenapax	IL2R; humanizowane IgG1	profilaktyka reakcji odrzucenia przeszczepu	1997*
Efalizumab	Raptiva	CD11a; humanizowane IgG1	łuszczyca plackowata	2003*
Tocilizumab	Actemra	IL6R; humanizowane IgG1	reumatoidalne zapalenie stawów	2010
Ustekinumab	Stelara	IL12/23; ludzkie IgG1	łuszczyca plackowata	2009
Omalizumab	Xolair	IgE; humanizowane IgG1	astma	2003
Natalizumab	Tysabri	α4 integryna; humanizowane IgG4	stwardnienie rozsiane	2004
Golimumab	Simponi	TNF; ludzkie IgG1	reumatoidalne i łuszczycowe zapalenie stawów, ZZSK	2009
Certolizumab pegol	Cimzia	TNF; humanizowane Fab' pegylowane	choroba Crohna	2008
Adalimumab	Humira	TNF; ludzkie IgG1	reumatoidalne zapalenie stawów	2002
Infliximab	Remicade	TNF; chimeryczne IgG1	choroba Crohna	1998
Abciximab	Reopro	GPIIb/IIIa; chimeryczne IgG1 Fab'	prewencja zakrzepów po zabiegach rewaskularyzacyjnych	1994
Denosumab	Prolia	RANK-L; humanizowane IgG2	osteoporoza	2010
Palivizumab	Synagis	RSV; humanizowane IgG1	zakażenia RSV	1998
Ranibizumab	Lucentis	VEGF; humanizowane IgG1 Fab'	AMD	2006

* Preparaty wycofane w USA.

mAbs w nefrologii



mAbs w nefrologii



Przeciwciała monoklonalne

Table 1. Monoclonal antibodies that are currently used in renal transplantation.

Name	Area of application	Origin	Target and mechanism of action	Dosing regimen	Main side effects
Alemtuzumab	Treatment of acute rejection Induction therapy	Rat, humanized	CD52 on mononuclear cells, depleting antibody	Single or double dose of 20–30 mg each iv. or sc. Pediatric dosing unknown	First-dose reaction after iv. administration, allergic reaction and increased incidence of infections
Basiliximab	Induction therapy	Mouse, chimeric	CD25 on T cells, nondepleting antibody	Two doses of 20 mg iv., 4 days apart. Pediatric dosing two doses of 10 mg	None
Rituximab	Blood group ABO-incompatible transplantation Desensitization Treatment of acute rejection Induction therapy	Mouse, chimeric	CD20 on B cells, depleting antibody	Single dose of 375 mg/m^2 or two doses of 1000 mg, 2 weeks apart. Pediatric dosing 375 mg/m^2	Mild cytokine release syndrome, allergic reaction, neutropenia
Eculizumab	Treatment and prevention of antibody-mediated acute rejection Treatment of post-transplant hemolytic uremic syndrome	Mouse, humanized	Complement C5, blocks formation of membrane attack complex	Variable; loading dose of 1200 mg and weekly doses of 900 mg. Pediatric dosing unknown, Phase II trial underway [104]	Insufficient data; increased risk of infection with encapsulated bacteria

iv.: Intravenous; sc.: Subcutaneous.

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Immunotherapy (2011) **3**(7), 871–880

ISSN 1750-743X

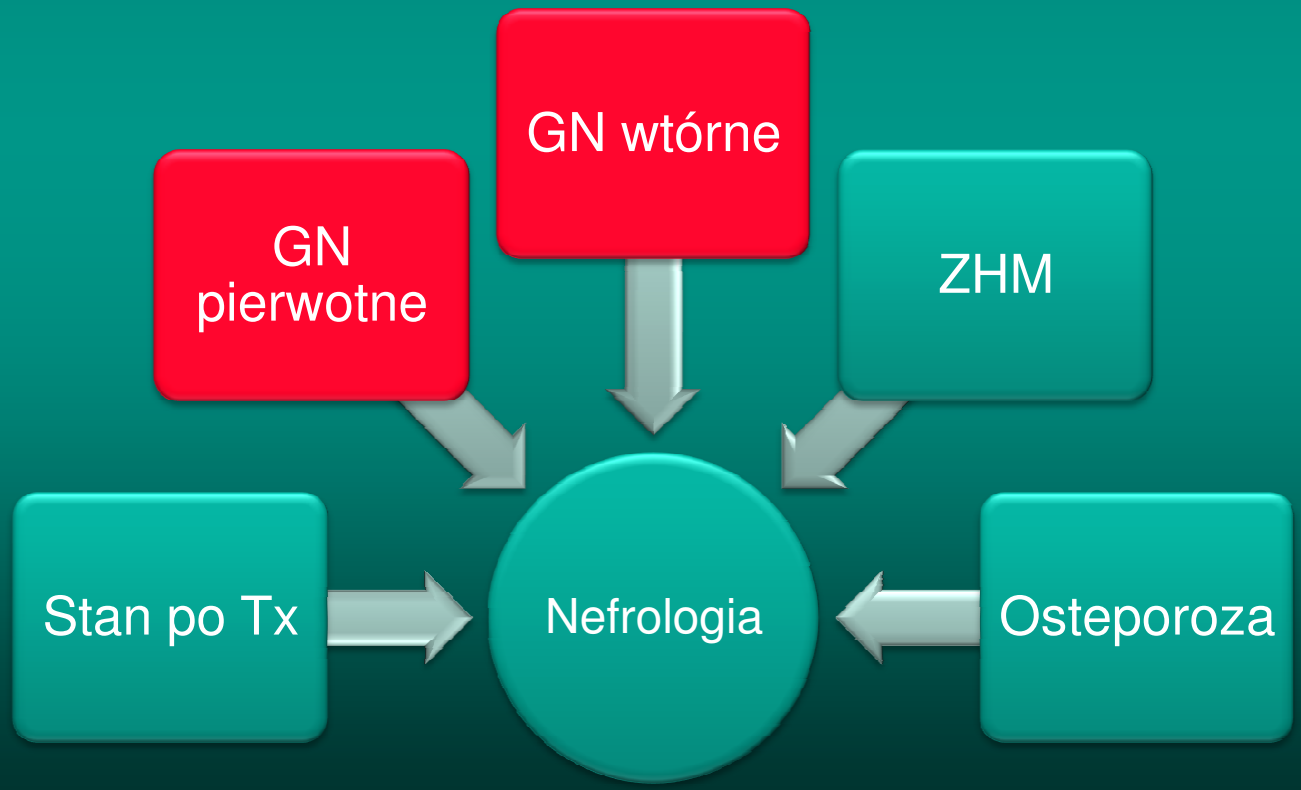
Przeciwciała monoklonalne

epratuzumab
humanizowane p-ciało anty-CD22

belimumab
ludzkie p-ciało anty-BLyS (B-cell-stimulating factor)

tocilizumab
humanizowane p-ciało anty-IL-6

mAbs w nefrologii



Przeciwciała monoklonalne

Materiał i metody:

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis

Andrew S. Bomback, Richard J. Smith,† Gaetano R. Barile,‡ Yuzhou Zhang,† Elliot C. Heher,§ Leal Herlitz,‖ M. Barry Stokes,‖ Glen S. Markowitz,‖ Vivette D. D'Agati,‖ Pietro A. Canetta,* Jai Radhakrishnan,* and Gerald B. Appel**

Wyniki:

- ↓Cr – 2
- ↓U_{prot}
- ↓zmian histologicznych

Przeciwciała monoklonalne

CLINICAL COMMENTARY www.jasn.org

Role of Rituximab Therapy in Glomerulonephritis

David Jayne

Renal Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom

Pediatr Nephrol
DOI 10.1007/s00467-012-2260-3

REVIEW

Indications for use and safety of rituximab in childhood renal diseases

Kjell Tullus · Stephen D. Marks

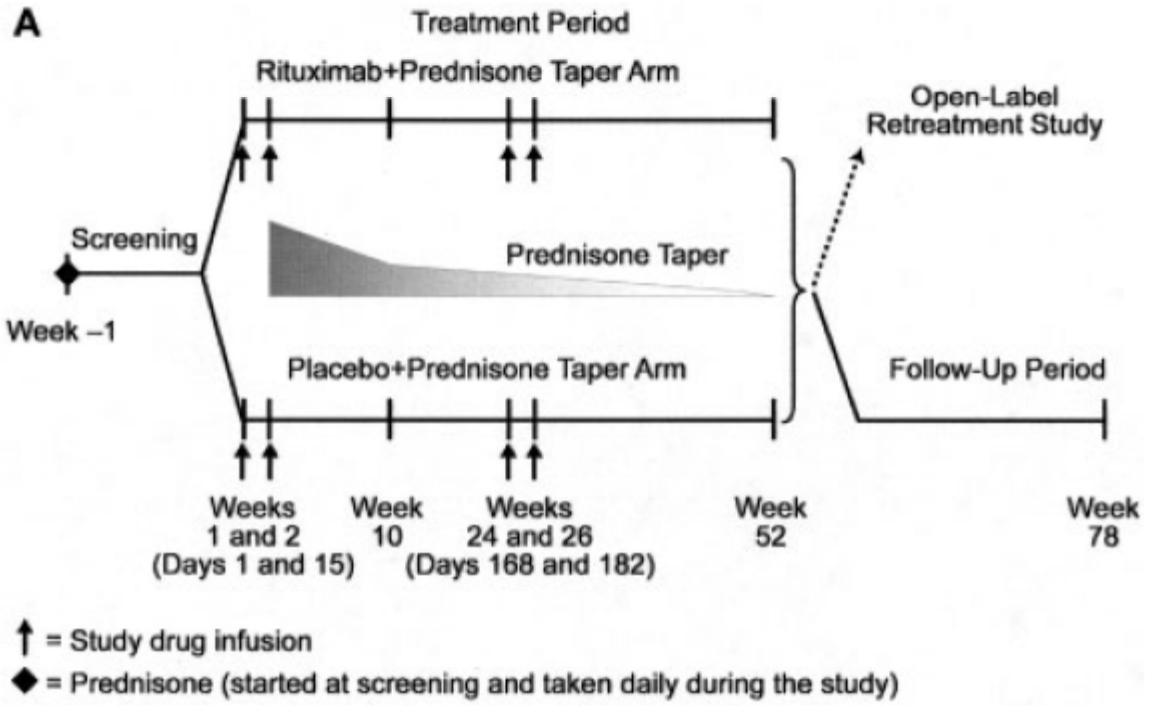
Table 1. Rituximab studies[a]

Study	Concomitant Treatments	Remission (Nephritis)	Serology Change[b]	Relapse
ANCA vasculitis				
Keogh *et al.* (2005)[18]	GC, PLEX	10/11 CR, 1/11 PR (4/4)	8/11 negative all decreased	2 (7, 12 mo)
Keogh *et al.* (2006)[25]	GC	10/10 CR (7/7)	6/10 negative all decreased	1 (9 mo)
Smith *et al.* (2006)[20]	GC, MMF	9/11 CR, 1/11 PR (6/6)	6/10 negative all decreased	6/10 (median 16.5 mo)
Stasi *et al.* (2006)[19]	GC	9/10 CR, 1/10 PR (6/6)	8/10 negative all decreased	3/10 (12, 16, 24 mo)
SLE				
Looney *et al.* (2004)[22]	GC, AZA, MTX, HCQ	13/18 CR or PR (4/6)	No significant change	4/11 (timing NR)
Gottenberg *et al.* (2005)[33]	NR	7/13 CR, 2/13 PR (2/4)	Variable	2/9 (9, 15 mo)
Sfikakis *et al.* (2005)[34]	GC	5/10 CR, 3/10 PR (8/10)	Decrease	3/8 (5, 5, 8 mo)
Smith *et al.* (2006)[20]	MMF, AZA GC	6/11 CR, 5/11 PR (6/6)	No significant change	7/11 (median 12 mo)
Vigna-Perez *et al.* (2006)[35]	GC, MMF, MTX, AZA	18/22 improved, 5/22 CR (12/22)	No significant change	NR
Nwobi *et al.* (2008)[36]	GC, MMF HCQ	7/18 CR, 10/18 PR (17/18)	Decrease	5/18
Podolskaya *et al.* (2008)[16]	GC, CYC AZA, MMF, HCQ	11/19 CR, 8/19 PR (15/15)	Decrease	NR
Ng *et al.* (2007)[14]	GC, CYC, HCQ	30/32 CR or PR (21/21)	Decrease	18/32 (mean 10 mo)
Lindholm *et al.* (2008)[15]	GC, CYC MTX, MMF	30/33 CR or PR (11/17)	Decrease	11/30
Membranous glomerulonephritis				
Fervenza *et al.* (2008)[11]	ACE/ARB	8/14 response	–	NR
Ruggenenti *et al.* (2006)[21]	ACE/ARB	14/23 response	–	2/9

[a]Clinical studies of rituximab in primary or secondary glomerulonephritis involving at least 10 patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AZA, azathioprine; CR, complete remission; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; NR, not reported; PLEX, plasma exchange; PR, partial remission.
[b]ANCA for ANCA vasculitis; anti-dsDNA for systemic lupus erythematosus (SLE).

Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus

The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial



Przeciwciała monoklonalne

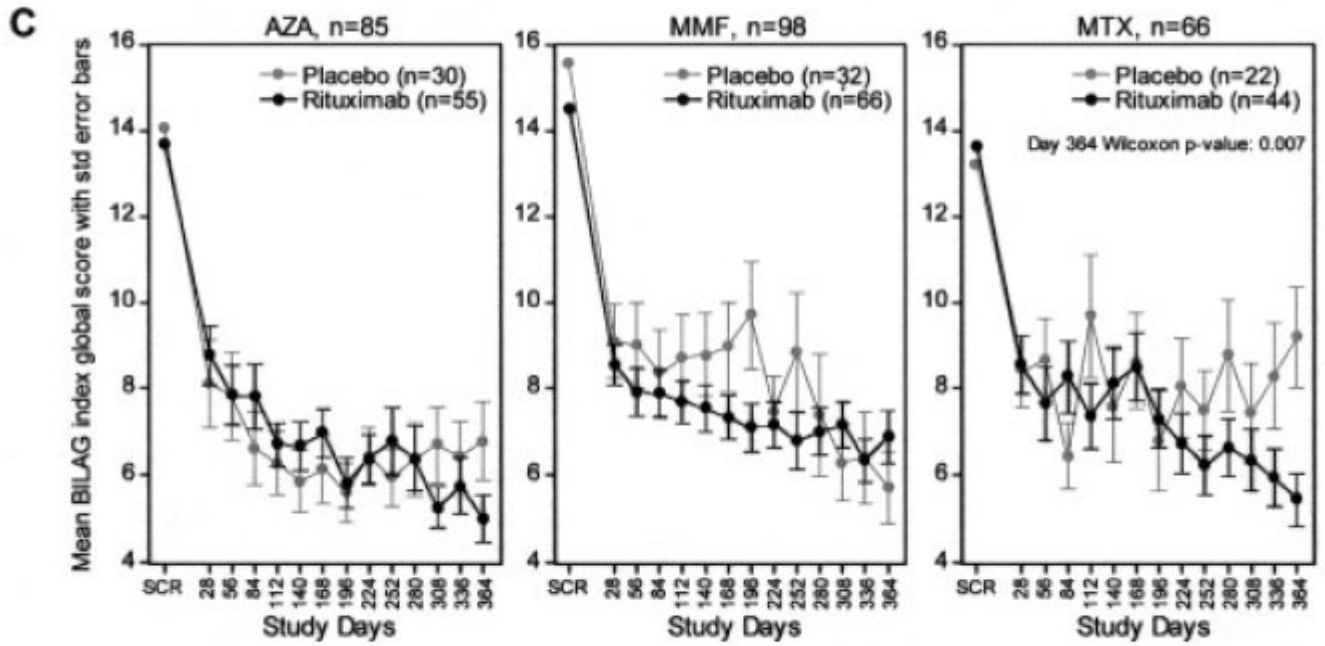
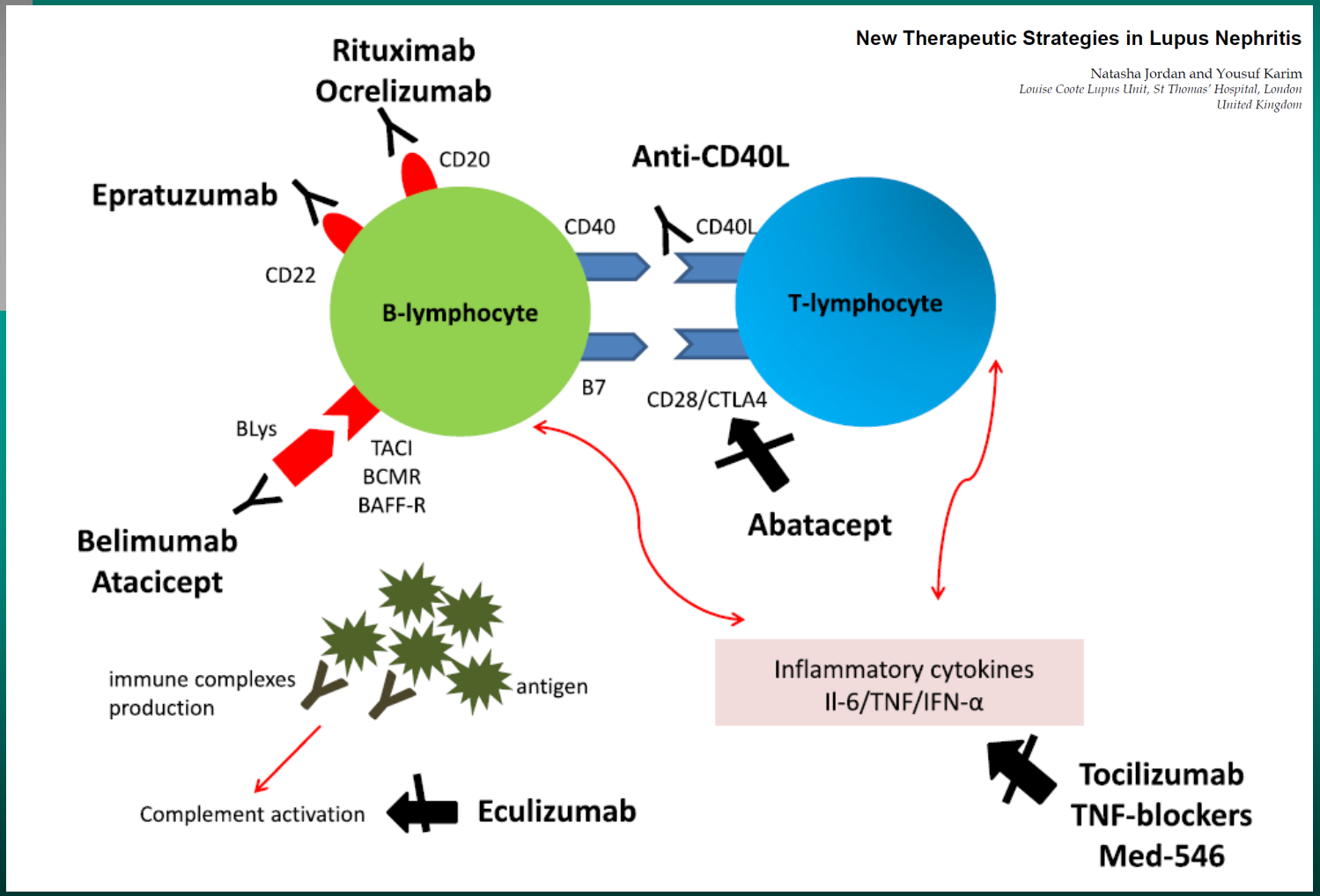


Figure 2. **A,** Proportion of patients experiencing a major clinical response (MCR), a partial clinical response (PCR), and no clinical response (NCR) at 52 weeks. **B,** Responders with African American/Hispanic backgrounds. **C,** Responders, according to the background immunosuppressive drug. BILAG = British Isles Lupus Assessment Group; AZA = azathioprine; MMF = mycophenolate mofetil; MTX = methotrexate.

Przeciwciała monoklonalne



Przeciwciała monoklonalne

Pediatr Nephrol (2013) 28:511–514
DOI 10.1007/s00467-012-2332-4

BRIEF REPORT

Late recovery of renal function by rituximab in a patient with Wegener's granulomatosis

Michal Malina · Betti Schaefer · Rüdiger Waldherr · Elke Wühl · Franz Schaefer · Claus Peter Schmitt

Przeciwciała monoklonalne

Table 2 Outcome in larger case series of rituximab treatment in children with steroid-dependent or frequently relapsing nephrotic syndrome

Author	Number of children	Full or partial response (*n*) (%)	Side-effects
Benz et al. [32]	1	1	None described
Guigonis et al. [33]	22	19 (85 %)	Five mild
			Four regarded as severe
			Atrial arrhythmia stopping spontaneously
			Malaise, transient bronchospasm
			Severe rotavirus gastroenteritis
			Transient neutropenia with gingivitis
Prytula et al. [34]	28	23 (82 %)	Data not separated on different diagnosis in the publication
			19 (27 %) of 70 showed side-effect
			Most common acute reaction to infusion one was a severe and life-threatening anaphylactic reaction
			Three severe infection
			Agranulocytosis with sepsis
			Two cases of pneumonia one of which with pseudomonas
Gulati et al. [35]	24	20 (83.3 %)	Three had mild infusion reactions
Kemper et al. [36]	37	26 (70.3 %)	No serious side-effects

Przeciwciała monoklonalne

Table 3 Outcome in larger case series of rituximab treatment in children with steroid-resistant nephrotic syndrome

Authors	Number of children	Full or partial response (n) (%)	Side-effects
Bagga et al. [38]	5	5 (100 %)	No severe
Prytula et al. [34]	27	12 (44 %)	See Table 2.
Gulatti et al. [35]	33	16 (48.4 %)	One mild infusion reaction

Efficacy and safety of rituximab treatment in children with primary glomerulonephritis

Jacek Zachwieja, Magdalena Silska, Danuta Ostalska-Nowicka, Jolanta Soltysiak, Katarzyna Lipkowska, Andrzej Blumczynski, Anna Musielak

Department of Pediatric Nephrology, Poznan University of Medical Science, Poznan - Poland

J Nephrol. 2012 Nov-Dec;25(6):

TABLE I
PROTEINURIA IN THE VARIOUS STAGES OF TREATMENT

Patient no., indication for treatment	Number of rituximab pulses	Output proteinuria (mg/kg per 24 hours) at start of treatment	Proteinuria 1 month after rituximab infusion (mg/kg per 24 hours)	Proteinuria 3 months after rituximab infusion (mg/kg per 24 hours)	Proteinuria 6 months after rituximab infusion (mg/kg per 24 hours)
1. SRNS	4	0	0	0	11
2. SRNS	4	75	37	4	0
3. SDNS	4	0	0	0	0
4. SRNS	1	0	0	0	0
5. SRNS	1	15	5	15	19
6. SDNS	1	0	0	0	0
7. SRNS	1	5	0	0	249
8. SRNS	4	27	20	9.4	8
9. SRNS	1	5	0	5	8.4
10. SRNS	1	0	0	5	0
11. SRNS	1	10	0	15.8	13.2
13. SRNS	1	5	0	0	10
14. SRNS	1	15	0	4.3	7.1
15. SRNS	1	0	0	0	0
16. SRNS	1	30	20	15	15

Efficacy and safety of rituximab treatment in children with primary glomerulonephritis

Jacek Zachwieja, Magdalena Silska, Danuta Ostalska-Nowicka, Jolanta Soltysiak, Katarzyna Lipkowska, Andrzej Blumczynski, Anna Musielak

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J Nephrol. 2012 Nov-Dec;25(6):

Conclusions

In conclusion, we postulate that alternative rituximab therapy should be taken into consideration in nephrotic patients not responding to standard therapy. In this group, the potential benefits of the therapy may outweigh the expected side effects.

REVIEW

Indications for use and safety of rituximab in childhood renal diseases

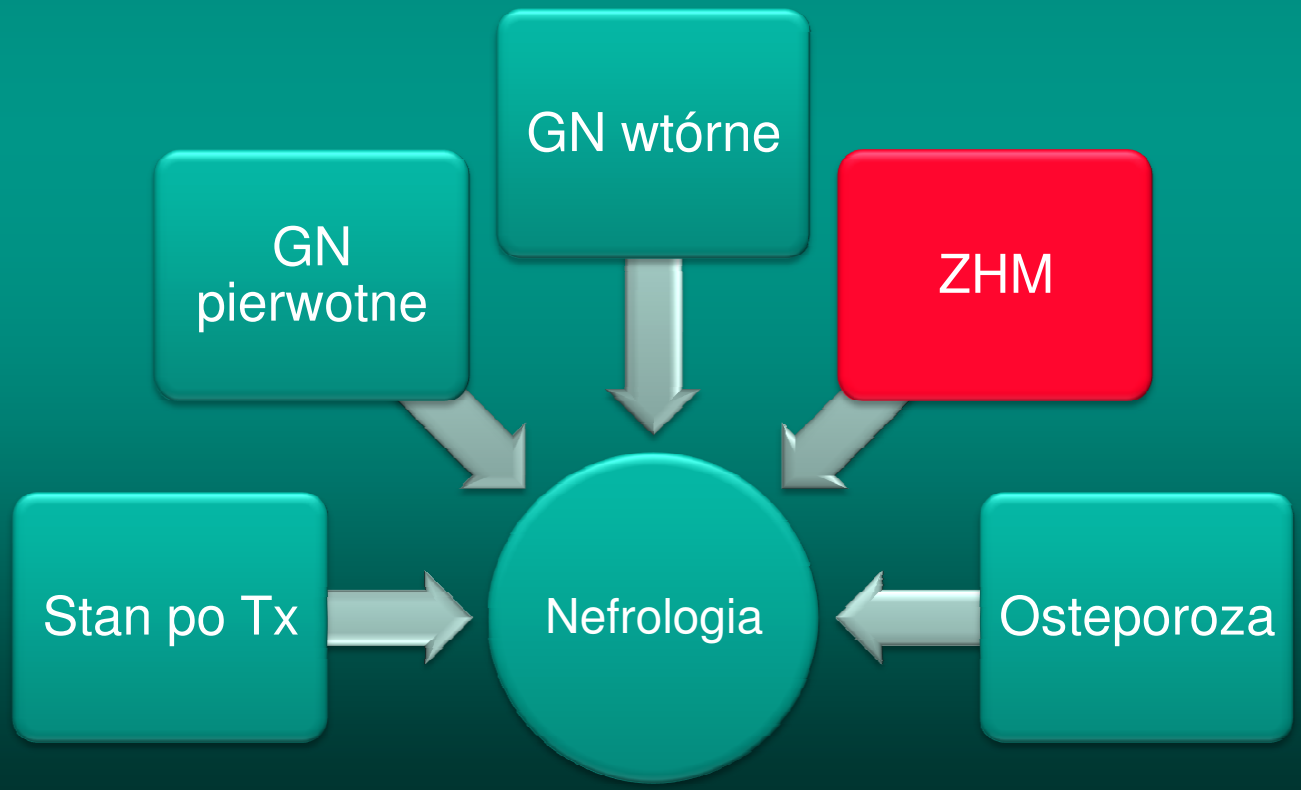
Kjell Tullus · Stephen D. Marks

Received: 2 May 2012 /Revised: 15 June

Conclusions

Rituximab has been used to treat an increasing number of different conditions in pediatric nephrology over the last decade. It has proven to be quite effective with a good side-effect profile in case series, although no randomized controlled trials currently exist for children. There is now a strong need to further explore and establish the role of rituximab in children with renal disease through proper trials.

mAbs w nefrologii



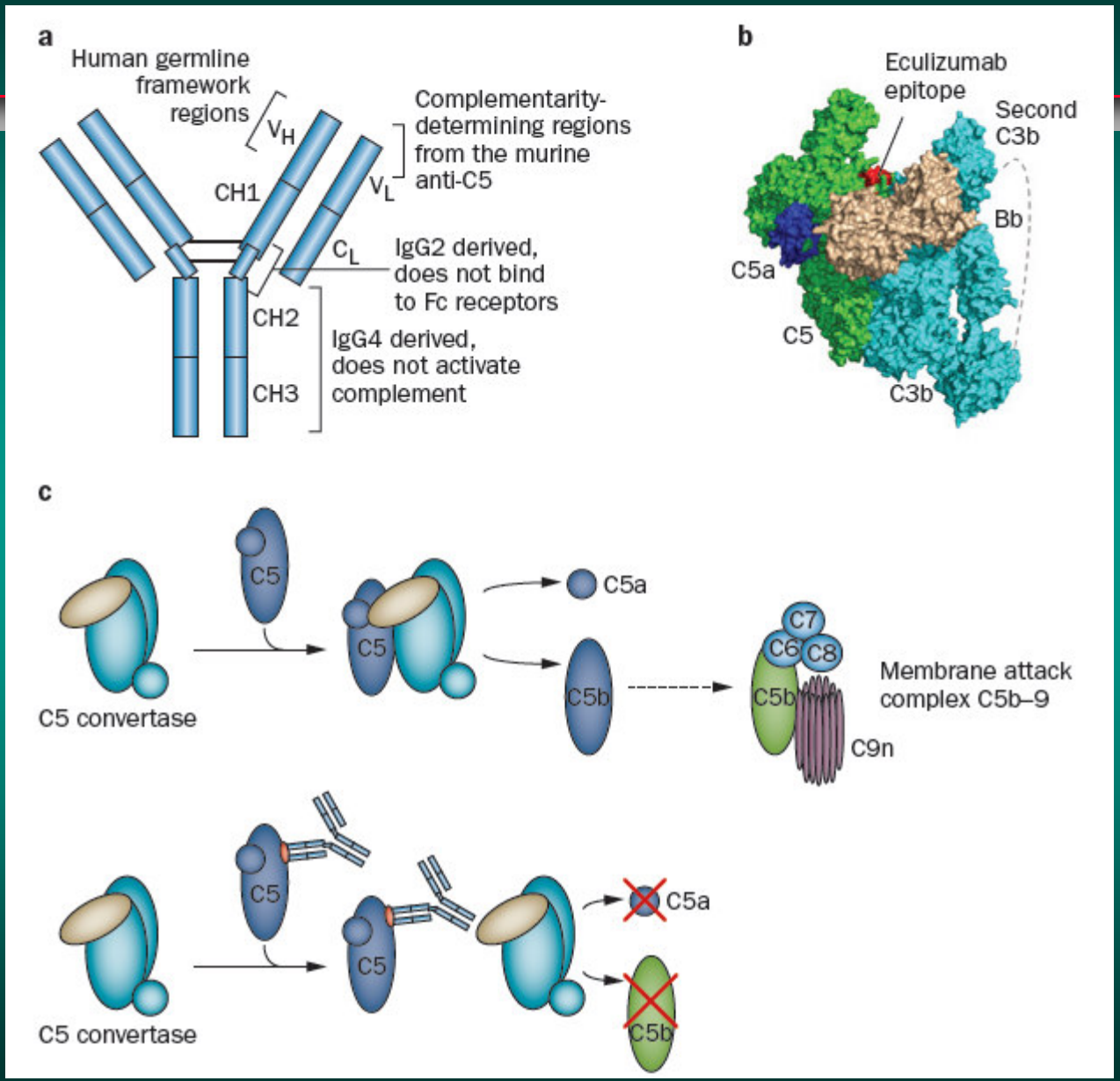
Przeciwciała monoklonalne

Complement Inhibitor Eculizumab in Atypical Hemolytic Uremic Syndrome

Christoph J. Mache,* Birgit Acham-Roschitz,* Veronique Frémeaux-Bacchi,†
Michael Kirschfink,‡ Peter F. Zipfel,§ Siegfried Roedl,* Udo Vester,‖ and Ekkehard Ring*

*Department of Pediatrics, Medical University Graz, Graz, Austria; †Service d'Immunologie Biologique, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, and Cordeliers Research Center, INSERM UMRS 872, Paris, France; and ‡Institute of Immunology, University of Heidelberg, Heidelberg, §Department of Infection, Hans Knoell Institute for Natural Products Research and Friedrich Schiller University of Jena, Jena, and ‖Clinic of Pediatric Nephrology, University of Duisburg-Essen, Essen, Germany

Clin J Am Soc Nephrol 4: 1312–1316, 2009. doi: 10.2215/CJN.01090209

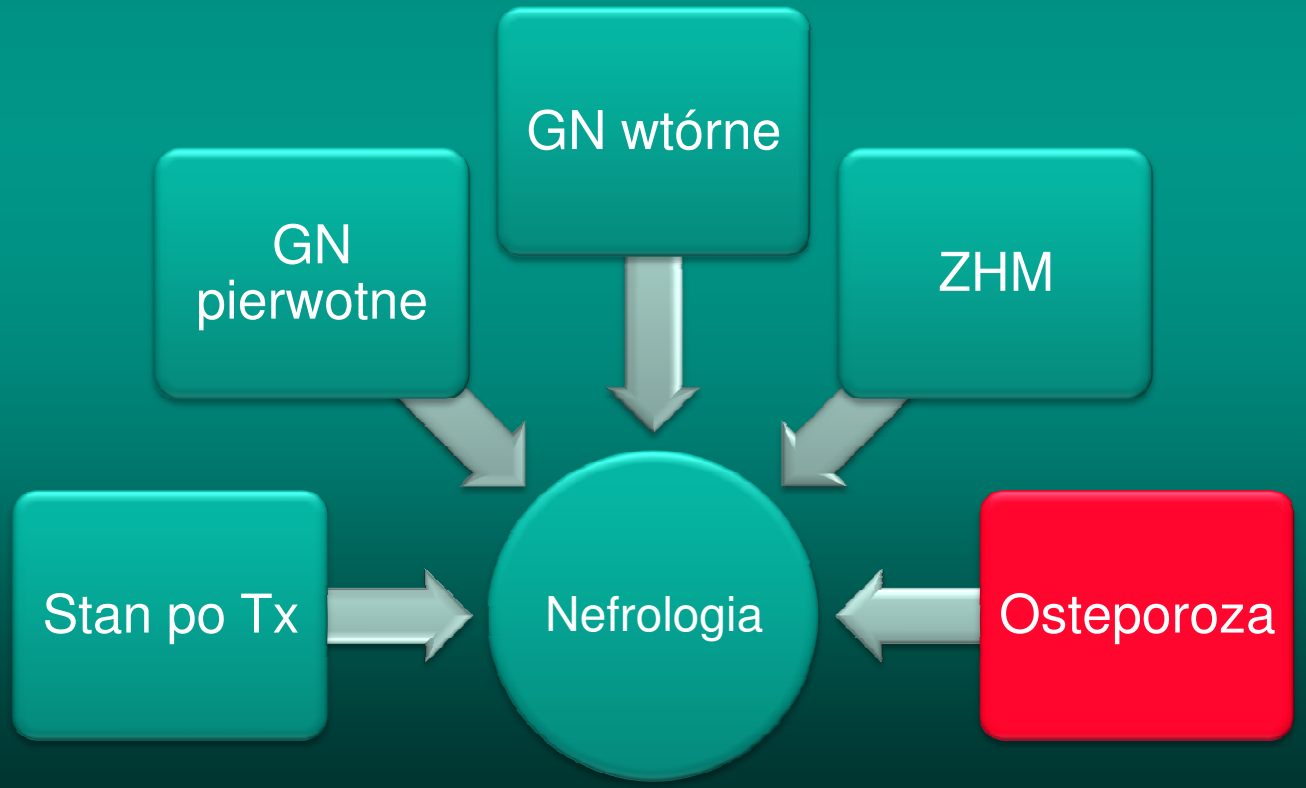

a
Human germline framework regions
V_H
V_L
Complementarity-determining regions from the murine anti-C5
CH1
C_L
IgG2 derived, does not bind to Fc receptors
CH2
CH3
IgG4 derived, does not activate complement
b
Eculizumab epitope
Second C3b
Bb
C5a
C5
C3b
c
C5
C5a
C5b
C7
C6
C8
C5b
C9n
Membrane attack complex C5b–9
C5 convertase
C5
C5a
C5b
C5 convertase

Przeciwciała monoklonalne

Table 2 | Clinical and genetic characteristics of 24 off-trial patients treated with eculizumab for overt aHUS

Patient characteristics	Children ($n=11$)	Adults ($n=13$)
Epidemiological data		
Median age at aHUS onset	0.9 years (range 0.02–8 years)	22.5 years (range 3–50 years)
Familial aHUS	2/10 (20%)	2/11 (18.2%)
Complement mutation identified	8/11(72.7%)	7/13 (53.8%)
CFH	6/11 (54.5%)	4/13 (30.8)
–C-terminal mutation and NAHR in *CFH*	3/4 (75.0%)*	3/4 (75%)
CFI	0/11 (0%)	1/12 (8.3%)
C3	2/11 (18.2%)	1/12 (8.3%)
CFB	0/11 (0%)	0/12 (0%)
MCP	0/11 (0%)	1/12 (8.3%)
Mutation not identified/not specified	3/11 (27.3%)	6/13 (46.2%)
At the time of the current aHUS episode		
aHUS in native kidneys	9/11 (81.8%)	5/13 (38.5%)
First episode of aHUS in native kidneys	4/9 (44.4%)	4/5 (80.0%)
aHUS in transplant kidneys	2/11 (18.2%)	8/13 (61.5%)
RTx with recurrence in previous graft	1/1 (100%)	5/5 (100%)
At the time of anti-C5 therapy		
First-line therapy for overt aHUS episode	0/11 (0%)	2/13 (15.4%)
Null or incomplete response to plasma therapy	10/11 (90.9%)	9/13 (69.2%)
Plasma dependence	1/11 (9.1%)	2/13 (15.4%)
Median age	4 years (range 0.1–15 years)	34 years (range 18–50 years)
Patients on dialysis	3/10 (30%)	3/12 (25%)
Mean ± SD day 0 creatinine level in off-dialysis patients	231 ± 158 μmol/l	366 ± 249 μmol/l
Median interval between aHUS and anti-C5	21 days (range 2–225 days)	30 days (range 1–420 days)
Response to anti-C5 therapy		
Normalization of aHUS-related haematological features	11/11 (100%)	13/13 (100)
Full recovery of baseline renal function	8/10 (80%)	4/13 (30.7%)
Decrease in creatinine level greater than 25%	9/10 (90%)	9/13 (69.2%)
Percentage reduction in creatinine level	63.3 ± 28.8	41.9 ± 29.5
Median follow-up‡	22 months (range 2.5–42 months)	15 months (range 2–49 months)
Mean ± SD creatinine level at last follow-up‡	53.9 ± 34.5 μmol/l	163.2 ± 96.2 μmol/l

mAbs w nefrologii



Przeciwciała monoklonalne

Denosumab for the prevention of osteoporotic fractures in postmenopausal women

This guidance was developed using the single technology appraisal process

NHS
National Institute for Health and Clinical Excellence

Przeciwciała monoklonalne - podsumowanie

- Ważny element w farmakoterapii
- Nadzieja na mniej uciążliwą, bardziej selektywną, ale także skuteczniejszą terapię
- Zmniejszenie uciążliwych i niepożądanych działań dla pacjenta
- Brak skuteczności we wszystkich przypadkach
- Istotne ograniczenie - bardzo wysoki koszt